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Physiological basis and Mechanism of Headache: Recent advances

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Abstract
Headache is a very common complaint for which a patient reports to the physician. It can cause discomfort in some patients whereas it can be a harbinger of some serious medical conditions in others. In our earlier review on headache published in the same journal, we had discussed some of the well established physiological basis and mechanisms behind different types of headaches. The aim of this review is to unravel some of the recent advances in the knowledge of the mechanisms of the various types of headache and also discuss about two lesser discussed types of headaches experienced by general population.
Keywords: *Headache, Migraine, Tension type Headache, Cluster headache, Pathophysiological mechanisms, Primary Exercise Headache, Menstrual Related Headache, Recent advances.*

Introduction

Headache is one of the most commonly reported medical symptom by the general population. It is an example of a medical condition which crosses national boundaries and all grades of socioeconomic strata in the population[2]. By its etiology, it can be caused due to a simple conditions such as stress of day-today life to more serious life threatening conditions such as subarachnoid haemorrhage[1]. The knowledge regarding the physiological basis and the mechanisms responsible for the different types of headache has improved drastically in the recent times and new mechanisms and factors responsible for the various types of headache are being unravelled every day.

Headache is a cause of enormous burden to the productivity of the society and the economy[3]. According to the World Health Organization, globally the prevalence of headache among adults is about 50%[2]. Almost 75% of adults of age group 18 to 65 years across the world have reported complaints of headache in the previous year[2]. The average prevalence of migraine is 18% across the lifetime, with its prevalence in children and adolescents being almost 7.7%[3]. The lifetime Prevalence of Tension type headache is about 52% and it is the most common type of headache reported[3]. In a community based study conducted in eastern India among subjects from the population aged between 20 to 50 years, it was estimated that the prevalence of migraine was 14.12% with the most susceptible age group being women aged 30 to 34 years[4]. Another study found a one year prevalence of 62% for primary headache in southern India[5]. As reported in our

earlier review[1], the most common types of headache are Migraine, Cluster headache and Tension Type headache which are collectively called as Primary headache disorders. In addition the mechanisms involved in the pathogenesis of two more less common types of headaches, Primary Exercise Headache (PEH) and Menstrual Related Headache (MRH) is also discussed in this review.

The aim of this review is to add to the existing knowledge of the pathophysiological mechanisms of the aforementioned types of headache. The mechanisms discussed in our earlier review has not been repeated, only new advances in knowledge have been elaborated in this review. This review could be a source to update oneself about the pathophysiological mechanisms of various types of headache in a concise manner.

Migraine

Genetic Component

In a recent Genome wide association study (GWAS)[6], 44 single nucleotide polymorphisms (SNPs) were shown to be associated with migraine without aura most of which were linked to vascular function while some of them were also related to metal ion homeostasis. In the Familial hemiplegic model, the role of genes namely CACNA1A,ATP1A2,SCN1A,Nav1.1 and glial Na^+K^+ATPases have been recently implicated all of which have been found to increase the availability of glutamate in the synaptic cleft[7]. CACNA1A gene mutation leads to increased glutamate release at the synapse due to increased influx of presynaptic calcium[8]. ATP1A2 gene mutation results in lesser electrochemical gradient of sodium ion which leads to inactivation of astrocyte glutamate transporters leading to accumulation of glutamate at synapse[9]. SCN1A gene mutation leads to alteration of high frequency discharge at glutaminergic synapse which increases the glutamate levels at the synapse[10]. The increased firing can also explain to an extent the susceptibility of the cortex for cortical spreading depression which is believed to be the mechanism for the *aura* of migraine[11,12].

Epigenetic Component

Very few studies on migraine are available with relation to the epigenetic aspect. In a recent GWAS of DNA-methylation in headache, two CpG sites were identified namely SH2D5 and NPTX2 genes[13]. The SH2D5 gene regulates synaptic plasticity by controlling the Rac-GTPase signaling[13]. The NPTX2 gene mediates the expression of pentraxin II protein which inhibits the excitatory synapse[13].

Brain Structural Component:

White matter lesions have been seen in female migraine patients with aura[14]. These lesions in the white matter have been shown to evolve over time i.e. become visible lesions from focal invisible microstructural changes[15]. Also they were found to be increased in number over time[16]. Grey matter changes involving reduction in the volume of thalamic nuclei with connection to limbic system including the central nuclear complex, anterior nucleus and lateral dorsal nucleus[17,18]. Patients with chronic migraine also demonstrated significant decrease in the volume of the hypothalamus[19]. In a recent study, it has been reported that high frequency transcranial magnetic stimulation of motor cortex can lead to sustained pain relief in migraine patients which points to the evidence of altered cortical excitability[39]in migraine.

Cluster Headache

Cluster headache which mimics other trigeminal autonomic cephalgias has been found to be associated with hypothalamic grey matter activation[20,21,22]. The A11 hypothalamic nucleus which is located in the PVN of caudal hypothalamus is believed to provide direct inhibitory dopaminergic projections to the spinal cord dorsal horn which is a site for gating of pain signals[23]. Alterations of the activity of this nucleus has been associated with headache[24]. Cluster

headache attacks are almost always associated with increase of plasma concentration of Vasoactive Intestinal Polypeptide(VIP)[25]. Further, in cluster headache which are associated with autonomic symptoms there is an increase in plasma concentrations of both VIP and PACAP38 (Pituitary adenylate cyclase activating polypeptide-38)[26,28]. Release of these substances leads to dilation of the intracranial vessels, extravasation of plasma proteins and release of various inflammatory mediators in the meninges[27,28].

Tension Type Headache

Immunological Component

Increase in the levels of IL-1β has been seen in patients of chronic TTH[29]. Increased levels of TNFα, IL-1 and IL-6 were also found to be increased in chronic TTH[30].

Peripheral Sensitization Component

There is an exaggerated response of neurons to thermal and chemical stimulation which is called as sensitization[31]. Activation of IL-1 receptor and increase of IL-6 production leads to increase in TRPV1 and TRPA1 channels which increases neuronal sensitivity[32]. Increased activity of macrophage causes release of PGE2 which is postulated to increase neuronal sensitivity through EP1-4 receptors[32]. Release of IL-17RA through its downstream signalling is also postulated to increase sensitivity[32].

Central Sensitization Component

Activation of microglia by various mediators like Casp6,ATP,CCL2,TNFα, CSF-1 and CGRP have been shown to be responsible for altering central transmission leading to central sensitization[32].

Transformation of Peripheral sensitization to Central sensitization:

It has been seen that activated immune cells are carried to the site of injury by blood stream. The activated immune cells initiate peripheral sensitization of nerve endings by mechanisms discussed above. In addition to this immune cells, glial cells, oligodendrocytes (IL-33) and nerve fibres form a pain network where central sensitization takes place mainly by activation of microglia and release of inflammatory mediators as mentioned earlier[31,33]. These mechanisms have been said to be responsible for the change of acute TTH to chronic TTH[31,35]. Increase in mitochondrial superoxide synthesis has also been seen in spinal cord which is said to be responsible for altering nociception and mediating hyperalgesia[34,35].

Psychological Component

The studies relating to the psychological component of TTH are very conflicting. One study showed that a very high proportion of cases of TTH patients showed correlation with presence of anxiety, depression and somatoform disorder[36]. Another study has also shown that TTH is intimately linked to both anxiety and depression where one may be leading to the other[37]. This is further substantiated by the finding where inhibition of right dorsolateral pre-frontal cortex by low frequency transcranial magnetic stimulation (TMS) led to pain relief by modulation of pain network[38].

Primary Exercise Headache (PEH)

Primary exercise headache is a type of headache which is precipitated by strenuous exercise without significant pathology[40]. The mechanisms postulated are the presence of incompetent jugular valves which can increase intrathoracic pressure leading to decrease in cerebral venous drainage which leads to a transient increase in cerebral blood flow leading to increase in intracranial pressure which leads to head pain[41]. Also it has been postulated that transient spikes in blood pressure during exercise in the presence of inefficient cerebral blood flow autoregulation can lead to variation in intracranial pressure consequently leading to pain[42].

Menstrual Related Headache (MRH)

Menstrual related headache is a very specific subtype of headache which is common in women generally between two days before the onset of menstruation and can last up to third day of menstrual bleeding[43]. The mechanism proposed for this kind of headache is decrease in the level of oestrogen during the late secretory phase of menstrual cycle leading to decrease in production of serotonin which in turn leads to increase in CGRP and Substance P from the trigeminal nerves[43,44]. These mediators are known to increase the sensitization of nerves, cause cerebral vasodilation and increase the blood-brain barrier permeability which leads to stimulation of meninges by inflammatory mediators resulting in headache by all of the aforementioned mechanisms[44]. There might be a role of genetic factors in MRH because of differential expression of protein channels and receptors in the cell membranes, the role of which are well known in the pathology of migraine[45].

Conclusion

Headache is a very frequently reported medical condition with a large impact on day to day life of sufferers. A proper diagnosis and appropriate classification according to the presenting features along with its pathophysiological underpinnings can help the physician to decide its management more effectively.

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